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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,359	06/23/2005	Eva Altmann	PA/4-32832A	3331

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EXAMINER	
TRUONG, TAMTHOM NGO	
ART UNIT	PAPER NUMBER
1624	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,359	ALTMANN ET AL.	
	Examiner	Art Unit	
	TAMTHOM N. TRUONG	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-13 and 17-28* is/are rejected.

7)☒ Claim(s) *14-16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/9/08, 6/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

Applicants' amendment of 10-9-08 has been fully considered. Claims 1-10 have been cancelled.

Claims 11-28 have been added.

New claims are drawn to species that are not taught or fairly suggested by the references of **Masai et. al.**, **Gamboni et. al.**, and **Yamamoto et. al.**

However, species still read on formula IV of copending application 10/480,559.

Therefore, the previous rejection of Obviousness-type Double Patenting is maintained herein.

Double Patenting

The **nonstatutory double patenting** rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-13 and 23-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25, 32 and 34 of copending Application No. **10/ 480,559**. Although the conflicting claims are not identical, they are not patentably distinct from each other because formula IV of the copending application embrace species of the instant claims 11-13, especially when formula IV has the following substituents:

a. R_1' is a C2-C7 alkenyloxy, or C2-C7alkynyloxy;

b. R_2" is aryl-methyl is substituted with a C1-C7 alkyl group;

c. R_3" is a C1-C7 alkyl group.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement: Claims 17-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of recited disorders, does not reasonably provide enablement for the prevention of said disorders, nor does it enable a compositions of matter capable of preventing any disorders. The specification does not enable

any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

(1) The breadth of the claims;
(2) The amount of direction or guidance presented;
(3) The state of the prior art;
(4) The relative skill of those in the art;
(5) The predictability or unpredictability of the art;
(6) The quantity of experimentation necessary;

[See ***Ex parte Forman***, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also ***In re Wands***, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: Claims 17-22 recite:

> 17. (New) A method for the prevention or treatment of osteoporosis, juvenile osteoporosis, menopausal osteoporosis, post-menopausal osteoporosis, post-traumatic osteoporosis, fractures, osteopathy, osteo-malacia, periodontal bone loss or bone loss due to arthritis or osteoarthritis; in which an effective amount of a compound according to claim 11, or a pharmaceutically acceptable acid addition salt thereof, is administered to a patient in need of such treatment.

The term "osteopathy" covers "cranial osteopathy" and "visceral osteopathy". The term "osteo-malacia" is a disorder of defective bone mineralization including hypophosphatemia, and rickets which is a disease caused by deficiency in vitamin D. The term "fractures" includes various type of bone injuries such as: Avulsion fracture; Greenstick fracture; Salter-Harris

fractures; Basilar skull fracture; Blowout skull fracture; Jefferson cervical fracture; Hangman's cervical fracture; Flexion teardrop fracture; rib fracture; sternal fracture; shoulder, arm and hand fractures; hip, leg and foot fractures, etc. Thus, the scope of claims 17-22 is unduly broad. Claims 23-28 are drawn to pharmaceutical composition asserted to have applicability in methods for the prevention of numerous bone related disorders.

The amount of direction or guidance presented:

The specification describes the following bioassays:

Inositol phosphate formation assay:

To determine antagonistic activity at the human parathyroid calcium-sensing receptor (PcaR), compounds are tested in functional assays measuring the inhibition of calcium-induced inositol phosphate formation in CCL39 fibroblasts stably transfected with human PcaR.

Cells are seeded into 24 well plates and grown to confluence. Cultures are then labelled with [^{3}H]inositol (74 Mbq/ml) in serum-free medium for 24 h. After labelling, cells are washed once with a modified Hepes-buffered salt solution (mHBS: 130 mM NaCl, 5.4 mM KCl, 0.5 mM $CaCl_2$, 0.9 mM $MgSO_4$, 10 mM glucose, 20 20 min. Thereafter, cells are extracted with 10 mM ice-cold formic acid and inositol phosphates formed are determined using anion exchange chromatography and liquid scintillation counting. tes r

Assay for intracellular free calcium:

An alternative method to determine antagonism at the PcaR consists in measuring the inhibition of intracellular calcium transients stimulated by extracellular calcium. CCL39 fibroblasts stably transfected with human PcaR are seeded at 40'000 cells /well into 96-well Viewplates and incubated for 24 hours. Medium is then removed and replaced with fresh medium containing 2 µM Fluo-3 AM (Molecular Probes, Leiden, The Netherlands), In routine experiments, cells are incubated at 37 °C, 5 % CO_2 for 1 h. Afterwards, plates are washed twice with mHBS and wells are refilled with 100 µl mHBS containing the test compounds. Incubation is continued at room temperature for 15 minutes. To record changes of intracellular free calcium, plates are transferred to fluorescence-imaging plate reader (Molecular Devices, Sunnyvale, CA, USA). A baseline consisting in 5 measurements of 0.4 seconds each (laser excitation 488 nm) is recorded. Cells are then stimulated with calcium (2.5 mM final), and fluorescence changes recorded over a period of 3 minutes.

The state of the prior art: Currently, the state of the art has commercial drugs such as Fosamax and Boniva which are used to treat osteoporosis, but they are not really for the prevention of bone disorders as recited in claim 17. As for fractures, the treatment usually involves a plaster or fiberglass cast, fracture implant, and hip replacement. Fractures are not known to be treated with mere medical agents, thus the state of the art does not support the method of prevention in the specific situations set forth in the claims.

The relative skill of those in the art: With the advanced training, the skilled clinician would still have to carry out extensive research to select an effective compound from the list of species recited in claim 11. Not only does one have to determine an IC_{50} value, but also *in-vivo* activity to establish an LD_{50}, therapeutic index and pharmacokinetic profile(s) for each compound. Given an extensive list of compounds, such a task would require a tremendous amount of effort, time and resource.

The predictability or unpredictability of the art and The quantity of experimentation necessary:

The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the *in-vitro* assay on the inositol phosphate alone does not warrant a protocol for preventing several bone disorders as claimed herein.

See ***Hoffman v. Klaus*** 9 USPQ 2d 1657, and ***Ex parte Powers*** 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, given the unpredictable nature of the art, and the vast number of compounds claimed herein, one skilled in the art will have to carry out undue experimentation to practice the method of prevention recited in claims 17-22.

Claim Objections

Claims 14-16 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

Tamthom N. Truong
Examiner
Art Unit 1624

3-6-09